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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. | |
|------------------------------|-------------|----------------------|---------------------|-------------------------|--|
| 10/677,063 | 10/01/2003 | Jennifer X. Qiao | PH 7500 NP | 8093 | |
| 23914 | 7590 | 07/20/2006 | EXAMINER | | |
| LOUIS J. WILLE | | | | BALLS, ROBERT J | |
| BRISTOL-MYERS SQUIBB COMPANY | | | | ART UNIT | |
| PATENT DEPARTMENT | | | | 1625 | |
| P O BOX 4000 | | | | PAPER NUMBER | |
| PRINCETON, NJ 08543-4000 | | | | DATE MAILED: 07/20/2006 | |

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|----------------------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/677,063 | QIAO ET AL. |
| | Examiner R. James Balls | Art Unit 1625 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 23 January 2006.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-22 is/are pending in the application.
 4a) Of the above claim(s) 11-14 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-10 and 14-22 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____.
 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

1. Claims 1-22 are pending.
2. This application claims benefit of 60/415,366 filed on October 2, 2002 and claims benefit of 60/417,208 filed on October 9, 2002.
3. Claims 1-10 and new Claims 15-22 are currently under examination. Claims 11-14 are withdrawn as being drawn to non-elected subject matter.

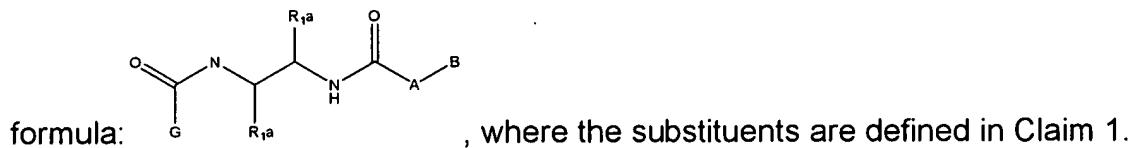
Election/Restrictions

4. The examiner required an election of species in the September 9, 2005 requirement for restriction. Applicants elected the structure of Example 15 in their February 27, 2006 response, with traverse, alleging that searching the entire scope of the claims would not impose an undue burden on the Office.

The five alternative core structures included in a Markush group of Claim 1 are not members of a true generic genus, as each alternative has a different chemical structure (there were six alternative core structures before applicants' amendment). All Markush alternatives need not be examined when the alternatives do not (1) share a common utility, and (2) a substantial structural feature essential to that utility. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). See MPEP 802.03. The five alternative structures differ in chemical arrangement, i.e. they do not share a common core structure. Also, one of the five alternative structures, the core structure encompassing applicants' elected species, functions as a therapeutic agent for inflammatory diseases,

a utility different than applicants' utility. See JP2003277340, Ishigaki et al, See CAS Accession No. 2003:767774, attached hereto. A search and examination of the entire scope of the claims cannot be made without a serious burden on the office. In this case, a *prima facie* showing of burden has been shown by the subject matter's separate status in the art and the different field of search required for each Markush alternative. Thus, the election of species is proper and hereby made FINAL.

The examination is limited to the elected species and the scope that read on the elected species. Applicants' elected species was not found in the prior art. Therefore, the examiner extended the search until he found compounds that read on broad Claim 1, i.e. the compounds of Dorsch et al. (WO0248099), which were applied in the previous Office Action. The current examination is therefore limited to the genus of



Claim Objections

5. Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The claims contain compounds that fall outside the scope of the genus under examination. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims contain subject matter that falls outside of the elected species and the genus of

compounds which encompass that species. See the "Election/Restriction" section above.

5. Claim 1 is objected to for including the word "of" before the phrase, "selected from." It appears that retention of the word "of" was an inadvertent mistake resulting from Applicants' February 27, 2006 amendment to the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-7 and 15-20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In the definition of "B" in claim 1 on the top of page 4 of the claims (and also in subsequent claims), the generic structure of B is listed with the proviso that "Z and B are attached to different atoms on A and that the A-X-N moiety forms other than a N-N-N group." It is unclear how this language relates to the rest of the claim. The only reference to a "Z" in the specification is on page 2, line 5, which is referring to a general structure disclosed in WO02/083630.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10 and 15-22 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for compounds where B is monocyclic does not reasonably provide enablement for compounds where B is bicyclic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. JP2003277340, ("Ishigaki et al."), which has a filing date of March 22, 2002, six months earlier than applicants' filing date, provides compounds that fall within applicants' claimed genus. Ishigaki et al.'s compounds have a B groups that is bicyclic. Applicants' claims encompass compounds where B is bicyclic but the specification only provides species where B is monocyclic. Ishigaki et al.'s bicyclic compounds are described as being integrin $\alpha 4$ inhibitors useable in the treatment of inflammatory diseases whereas applicants' monocyclic compounds are disclosed as being anticoagulant agents for the treatment of thromboembolic disorders.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be

described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Courts rely on the following factors set out in *In re Wands* to determine whether undue experimentation is required to practice a claimed invention, i.e. whether the claimed invention is enabled: (a) The breadth of the claims; (b) The nature of the invention and predictability in the art; (c) The state of the prior art; (d) The level of one of ordinary skill; (e) The existence of working examples; and (f) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.* The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *id.* at 1407.

The analysis is applied to the instant case.

- (a) The claims are drawn to compounds where B is both a mono and bicyclic ring system.
- (b) The invention is physiological in nature as it is directed toward pharmaceuticals and treating diseases with those pharmaceuticals, an art which is highly unpredictable. “[T]he scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered to be an unpredictable factor. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In the highly unpredictable pharmaceutical art, the required disclosure is greater than for the disclosure of an invention involving predictable factors

such as mechanical or electrical elements. *In re Vaeck*, 20 USPQ 2d 1438 (CAFC 1991).

(c) The state the art is such that compounds where B moiety is bicyclic have a different utility than when the B moiety is monocyclic. See JP2003277340, Ishigaki et al, See CAS Accession No. 2003:767774, attached hereto. The prior art teaches that compounds where B is bicyclic function as adhesion molecule inhibitors for the treatment of inflammatory diseases.

(d) The level of skill required to practice the invention is high due to its pharmaceutical nature.

(e) The specification contains no working examples of B being a bicyclic moiety.

(f) The quantity of experimentation necessary to make or use the disclosed invention is high, based on the unpredictability of the art, the limited guidance in the specification, and the lack of direction and working examples. A person of ordinary skill in the art would be subjected to undue experimentation in order to make and use the invention, and therefore, the invention is not enabled as claimed.

Rejoinder

Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP §821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is *presented prior to final rejection or allowance*, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process

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claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai; In re Brouwer* and 35 U.S.C. §103(b)," 1184 O.G. 86 (March 26, 1996).

Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. *Applicants are reminded of propriety of process of use claims in consideration of the "reach-through" format, which is drawn to mechanistic, receptor binding or enzymatic functionality. Reach-through claims are considered lacking of descriptive and enabling support from the specification. Thus, rejoinalble process of use claims are those with particular disease named with efficacy support from the specification for treating the particular disease. Failure to do so may result in a loss of the right to rejoinder.*

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Non-elected Claims 11-14 are drawn to methods of treating thromboembolic disorders and not currently under examination. However, in the event that the product claims become allowable, the methods claims will be rejoined as long as they are free of 35 U.S.C. §112 issues. At present, the claims are drawn to treating a wide range of thromboembolic disorders including, for example, myocardial infarction. The Cecil Textbook of Medicine explains, "Myocardial infarction is the term used to describe irreversible cellular injury and necrosis occurring as a consequence of prolonged ischemia." Wyngaarden & Smith, CECIL TEXTBOOK OF MEDICINE 247 (Sixteenth Edition). Based on the information in the specification, it is not clear how the instant compounds would treat irreversible cellular injury and necrosis, i.e. myocardial infarction. Instead, it seems the compounds would prevent the formation of thrombus

following, a procedure where blood is exposed to an artificial surface. See the assay on page 77.

Conclusion

9. No Claims are allowed.
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to R. James Balls whose telephone number is (571) 272-7997. The examiner can normally be reached on Mon - Fri 8:00am - 4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tom McKenzie can be reached on (571) 272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

R. James Balls
July 11, 2006



Celia Chang
Primary Examiner
Art Unit 1625